REMARKS

Claims 1-41 were pending in this application. Claims 3-4, 16-26, 29, 31-34 and 36-41 have been withdrawn by the Examiner as being drawn to non-elected inventions. Applicants have cancelled claims 2 and 28, without prejudice, and fully reserve the right to prosecute the subject matter of the cancelled claims in one or more related applications. Applicants have also amended claims 1 and 27 to clarify the presently claimed invention. Specifically, claims 1 and 27 have been amended to recite that steps (a) and (b) are conducted before the harvesting step (c). Support for the amendment can be found in the specification at, *inter alia*, page 3, lines 28-29. No new matter has been added.

Upon entry the present amendments, claims 1, 3-27 and 29-41 will be pending in this application.

I. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

Claims 1-2, 5-15, 27-28, 30 and 35 are rejected under 35 U.S.C. § 112, first paragraph (Section § 112, ¶1), because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Specifically, the Examiner alleges that the specification does not reasonably provide enablement for a method for producing a decellularized extracellular matrix containing vascular endothelial growth factor ("VEGF") or for producing a tissue regeneration scaffold for implantation into a patient, wherein the method comprises: (a) conditioning bone marrow of human donor to produce VEGF in an amount different than the amount of VEGF that the bone marrow would produce absent the conditioning by transfecting the bone marrow with any nucleic that encodes VEGF by any route of administration at any site in the human donor; (b) allowing the conditioned bone marrow to produce the VEGF; then (c) harvesting the conditioned bone marrow from the human donor; and (d) decellularizing the conditioned bone marrow to obtain the extracellular matrix material containing the VEGF (elected invention with elected species). For the following reasons, Applicants disagree.

1. The Legal Standard

The enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph, that the specification describes (1) how to make and (2) how to use the invention. *See* MPEP § 2164. The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent

specification coupled with information known in the art at the time the patent application was filed. *United States v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Enablement is not precluded even if some experimentation is necessary. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983).

By definition, undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 443 F.2d 1386, 1392, 170 U.S.P.Q. 276, 279 (CCPA 1971). The factors that are relevant in determining what constitutes undue experimentation as set forth by the Federal Circuit (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)) include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." Any conclusion of nonenablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. *In re Wands*, 858 F.2d 731, 740, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988).

The Patent Office must establish a *prima facie* case of non-enablement in order to properly reject a claim on that basis. "When rejecting a claim under the enablement requirement of § 112, the Patent Office bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention in the specification of the application..." *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The Patent Office's *prima facie* case should address each of the *Wands* factors since "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors while ignoring one or more of the others." *See* MPEP § 2164.01(a), citing *Wands* at 1407. Where the Patent Office does not provide evidence regarding one or more *Wands* factors, applicant presumes that such factors support the conclusion that the claims at issue are fully enabled.

2. The Specification Enables the Methods of the Present Invention

In the non-final Office Action mailed November 21, 2006, the Examiner alleges that when read in light of the specification, the sole purpose for a decellularized extracellular matrix material containing a biological material generated or produced by the instantly claimed invention is for treatment purposes such as repairing, regenerating or strengthening tissue or organs *in vivo*. The Examiner contends that it would require undue experimentation for a skilled artisan to make and use the elected invention because (1) at the filing date of the present application, the prior art does not teach the elected species of the claimed methods (*i.e.*, genetically modifying bone marrow of a human donor *in vivo* with a nucleic acid encoding VEGF, and subsequently decellularizing and harvesting the genetically modified bone marrow and using the resulting decellularized extracellular matrix material for repairing, regenerating or strengthening tissue or organ *in vivo*); (2) at the filing date of the present application, the attainment of any therapeutic effect in any patient via gene therapy was and remains highly unpredictable; and (3) the specification fails to provide (a) any guidance for a skilled artisan or (b) working examples on how to overcome the hurdle of *in vivo* vector targeting to desired tissues/organs so that an efficient gene delivery can be attained in the tissue/organ.

The rationale underlying the Examiner's rejection appears to be based on the assumption that the use of the decellularized extracellular matrix material produced by the claimed methods is ineffective. However, Applicants submit that *effective* use of the product produced by the claimed method is not required by Section 112, ¶1, for the determination of enablement of the claimed method. The enablement requirement merely requires that the specification teaches one skilled in the art *how* to use the invention. The Examiner has broadened the enablement requirement under Section 112, ¶1, to require that the use be effective. This is improper.

The specification clearly teaches that the decellularized extracellular matrix material produced by the claimed methods can be used by direct injection or implantation into a subject, as well as used to form a tissue regeneration scaffold or to coat or construct a medical device for insertion or implantation into a subject (*e.g.*, page 3, lines 7-18; page 5, line 3, to page 6, line 5). The effectiveness of the decellularized extracellular matrix material produced by the claimed methods at repairing, regenerating or strengthening tissue or organs *in vivo* is irrelevant to the determination of whether the claimed methods is enabled.

In fact, Applicants submit that the Examiner has not made an enablement rejection over the *claimed* method. "The invention that one skilled in the art must by enabled to make and use is *that defined by the claims*. See MPEP § 2164 (emphasis added). An enabling description for a process or method requires sufficient disclosure as to "how to carry out *the claimed process*." *In re Barrett*, 440 F.2d 1391, 1392 (emphasis added).

Amended claims 1 and 27 are directed to methods for producing a decellularized extracellular matrix material containing a biological material, and claim 35 is directed to a method for producing a tissue regeneration scaffold for implantation into a patient comprising the same conditioning, producing, harvesting, and decelluarizing steps used in the methods of amended claims 1 and 27. The claimed method does not require that an effective amount of biological material is produced by the transfected human bone marrow. Nor are the claimed methods directed to treating, repairing, regenerating, or strengthening tissue *per se*. Instead, the sole purpose of the invention is to *produce* the decellularized extracellular matrix material or a tissue regeneration scaffold comprising the decellularized extracellular matrix material. To "produce" means "to manufacture," "to create" and "to make"(see Exhibit 1, pages 1091-1092 of The American Heritage College Dictionary). Nowhere in the claims does it require that the decellularized extracellular matrix material or tissue regeneration scaffold produced by the claimed method to be used for any purposes, much less the purpose alleged by the Examiner (*i.e.*, repairing, regenerating or strengthening tissue or organs *in vivo*).

As previously discussed on pages 10-13 of the Amendment filed February 21, 2006, which is incorporated by reference herein in its entirety, the instant specification fully enables one skilled in the art on how to make the invention commensurate in scope with the claims without undue experimentation. For example, the specification also clearly teaches and fully describes how to culture the conditioned body tissue and monitor the effects of conditioning (see specification, *e.g.*, Sections 4.1.3 and 4.1.4 at pages 24-25), how to decellularize the conditioned body tissue (see specification, *e.g.*, Section 4.1.5 at pages 26-30), and how to make a tissue regeneration scaffold from the decellularized extracellular matrix material (see specification, *e.g.*, Section 4.2.3 at page 35).

The instant specification also fully enables one skilled in the art on how to use the invention commensurate in scope with the claims without undue experimentation. For example, the specification describes many ways of transfecting a body tissue with a nucleic acid that encodes a biological material of interest (see specification, *e.g.*, Section 4.1.2.1 at pages 14-20).

The Examiner's attention is respectfully directed to Chen *et al.* ("Lentiviral vector transduction of hematopoietic stem cells that mediate long-term reconstitution of lethally irradiated mice." Stem Cells. 2000;18(5):352-9, "Chen," a copy of which is included in Exhibit 2), which describes efficient gene delivery into murine stem cells with lentiviral vectors (see Chen, Abstract). Contrary to the Examiner's allegation, not only does the specification provides ample guidance for a skilled artisan on how to overcome the hurdle of *in vivo* vector targeting to desired tissues/organs so that an efficient gene delivery can be attained in the tissue/organ, and at the time of the invention, one skilled in the art would know how to attain efficient gene delivery in a human bone marrow tissue. In fact, the Examiner acknowledges that the delivery of a recombinant vector into a body tissue may be well established (see final Office Action mailed May 22, 2006, page 11, ¶2, lines 2-3).

In response to Applicants' remarks in the Amendment filed February 21, 2006, the Examiner mischaracterizes the issue of transfecting a body tissue with a nucleic acid encoding a biological material of interest and alleges that "it is not a matter of simply delivering a nucleic acid construct to transfer a body tissue. The issue involves how many cells in the targeted body tissue being transfected and most importantly whether an effective level or amount of the encoded biological material of interest could be expressed and produced by transfected cells so that it can be incorporated into the extracellular matrix of the body tissue, and the subsequently harvested and decellularized extracellular matrix could yield any therapeutic effect in repairing, regenerating or strengthening tissue or organs *in vivo* as contemplated by Applicants."

The elected species of the claimed methods includes a step (*i.e.*, step (b)) which requires the induction and/or alteration of gene product expression in the conditioned body tissue. However, as discussed above, the claimed methods are not directed to gene therapy *per se*, and thus, the predictability or unpredictability of the art with respect to gene therapy is irrelevant as to the determination of whether the claimed methods are enabled. Nevertheless, Applicants submit that at the time of the invention, successes in the field of gene therapy were known to one skilled in the art (see, *e.g.*, Helm *et al.*, "Gene-based Therapies for the Induction of Spinal Fusion." Neurosurg Focus. 2001;10(4):E5, "Helm," a copy of which is included in Exhibit 3). Based on Helm, which discusses the successful use of gene therapy in inducing spinal arthrodesis in athymic nude animals, Applicants submit that one skilled in the art, at the time of invention, would know how to determine the number of cells in a targeted body tissue being transfected with a nucleic acid encoding a biological material of interest

and the level or amount of the encoded biological material of interest expressed and produced by the transfected cells. Applicants submit that, together, the teaching of the specification, the nature of the invention, and the knowledge available in the field (*e.g.*, Chen and Helm), enables one skilled in the art to practice the claimed invention without undue experimentation. The absence of an illustrative examples is not determinant on whether undue experimentation is required. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971).

Applicants respectfully point out that the Examiner did not analyze three *Wand* factors, *i.e.*., (1) the quantity of experimentation necessary, (2) the nature of the invention, and (3) the relative skill of those in the art. "The examiner's analysis must consider all the evidence related to *each* of these factors, and any conclusion of nonenablement must be based on the evidence as a whole." *In re Wands*, 858 F.2d at 740 (emphasis added). Where the Patent Office does not provide evidence regarding one or more *Wands* factors, Applicants presume that such factors support the conclusion that the claims at issue are fully enabled.

Applicants submit that when all of the *Wands* factors are considered, one of ordinary skill in the art can determine without undue experimentation how to make and use the presently claimed methods. Applicants submit that in view of the present specification and the knowledge in the art, the skilled artisan will be able to make a decellularized extracellular matrix material containing a biological material using, for example, a vector to transfect the human bone marrow with a nucleic acid that encodes VEGF. Moreover, Applicants submit that in view of the present specification and the knowledge in the art, the skilled artisan will also be able to use the decellularized extracellular matrix material, for example, to produce the claimed regeneration tissue scaffold. If a statement of utility in the specification contains within it a connotation of how to use, the enablement requirement of how to use under 35 U.S.C. § 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). Accordingly, the instant specification fully enables one of skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation.

For the foregoing reasons, Applicants respectfully request that the claim rejections under Section §112, ¶1, be withdrawn.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 1, 5, 7-12, 14-15 and 27 remain rejected under 35 U.S.C. § 102(b) ("Section 102(b)") as allegedly being anticipated by U.S. Patent No. 5,830,708 to Naughton ("Naughton"). Specifically, the Examiner alleges that the scope of the claims as written encompasses the possibility that steps (a) and (b) can be conducted after the harvesting step (c); which means that after harvesting a body tissue from a donor animal, the harvested body tissue is then conditioned and allowed to produce a biological material.

Although Applicants do not agree and in no way acquiesce with the rejection, solely to expedite prosecution and obtain coverage for certain embodiments of the present invention, claims 1 and 27 have been amended to include the subject matter of claims 2 and 28, respectively, which were not rejected by the Examiner as being anticipated by Naughton. As amended, claims 1 and 27 recite that steps (a) and (b) are conducted before the harvesting step (c). Applicants respectfully request that the Examiner reconsiders the rejection in view of the amendments.

"A claim is anticipated only if *each and every* element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987) (emphasis added).

As amended, the claimed method clarifies that the body tissue is conditioned and allowed to produce the biological material *before* it is harvested and decellularized. Thus, the decellularized extracellular matrix material produced by the claimed method is collected from a body tissue created *in vivo*. In contrast, the decellularized extracellular matrix material disclosed in Naughton is isolated from a stromal tissue created *in vitro* (see discussion regarding Naughton in the Amendment filed on February 21, 2006 at pages 14-15, which is incorporated by reference herein). Since Naughton uses a different starting material to produce the decellularized extracellular matrix material than that used in the claimed method, Naughton fails to teach or suggest the methods of amended claims 1 and 27.

Claims 5, 7-12 and 14-15 are dependent on amended claim 1 and thus, incorporate the limitations of amended claim 1. As such, Naughton also does not anticipate claims 5, 7-12 and 14-15.

For the foregoing reasons, Applicants respectfully request that the claim rejections under Section 102(b) be withdrawn.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 1, 13, 27 and 30 remain rejected under 35 U.S.C. § 103(a) ("Section 103(a)") as allegedly being unpatentable over Naughton in view of International Publication No. WO 98/39035 to Herlyn *et. al.*("Herlyn").

Although Applicants do not agree and in no way acquiesce with the rejection, solely to expedite prosecution and obtain coverage for certain embodiments of the present invention, claims 1 and 27 have been amended to include the subject matter of claims 2 and 28, respectively, which were not rejected by the Examiner as being unpatentable over Naughton in view of Herlyn. As amended, claims 1 and 27 recite that steps (a) and (b) are conducted before the harvesting step (c). Applicants respectfully request that the Examiner reconsiders the rejection in view of the amendments.

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. See *In re Bell*, 26 U.S.P.Q.2d 1529, 1530 (Fed. Cir. 1993); MPEP 2142. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. See *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). Second, there must be a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Third, the prior art reference(s) must teach or suggest all the claim limitations. *Litton Indus. Products, Inc. v. Solid State Systems*, 755 F.2d 158, 164 (Fed. Cir. 1985). The teaching or suggestion to make the claimed combination and reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). The Federal Circuit has clearly stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d at 1075.

Applicants submit that the rejection under Section 103(a) is in error because the Patent Office has failed to establish a *prima facie* case of obviousness. The cited references do not teach or suggest all the claim limitations. In particular, the references, either alone or together, do not teach or suggest a method for producing a decellularized extracellular matrix material containing a biological material, wherein said method comprises (a) conditioning body tissue to produce a biological material in an amount different than the amount of the

biological material that the body tissue would produce absent the conditioning; (b) allowing the conditioned body tissue to produce the biological material; followed by (c) harvesting the conditioned body tissue from the donor animal; and (d) decellularizing the conditioned body tissue to obtain the extracellular matrix material containing the biological material, wherein steps (a) and (b) are conducted before the harvesting in step (c), as recited in amended claims 1 and 27.

As discussed above, Naughton does not teach or suggest decellularized extracellular matrix material that is produced by a body tissue created *in vivo*. Instead, Naughton discloses producing decellularized extracellular matrix material from a body tissue created *in vitro*.

Herlyn does not cure the deficiency of Naughton. Herlyn never mentions decellularizing any body tissue to obtain a decellularized matrix material, much less teach or suggest decellularizing a body tissue created *in vivo*. As such, Naughton and Herlyn, either alone or in combination, do not teach or suggest the methods of amended claims 1 and 27, and their dependent claims 13 and 30, respectively.

For the foregoing reasons, Applicants respectfully request that the claim rejections under Section 103(a) be withdrawn.

CONCLUSION

Applicants respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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